DOSAGE FORMS: PARENTERALS

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INTRODUCTION

Parenteral is derived from the two words "para" and "enteron" meaning to avoid the intestine. Parenteral articles are defined according to the USP 24/NF19 "as those preparations intended for injection through the skin or other external boundary tissue, rather than through the alimentary canal, so that the active substances they contain are administered using gravity or force directly into a blood vessel, organ, tissue, or lesion. Parenteral products are prepared scrupulously by methods designed to ensure that they meet pharmacopeial requirements for sterility, pyrogens, particulate matter, and other contaminants, and, where appropriate, contain inhibitors of growth of microorganisms. An injection is a preparation intended for parenteral administration and/or for constituting or diluting a parenteral article prior to administration" (1). Parenteral drug administration is an attractive route of administration when oral administration is contraindicated, and it has been traditionally used in institutional settings. With an increasing interest in reducing overall health care costs and with the development of new biotechnologically derived compounds and improved and novel infusion-related technologies, parenteral products have become an important component in the care of patients in hospitals and the home health care setting. In the present article, information will be presented on history and the following: the use of parenterals in health care, the advantages and disadvantages of using parenterals, routes of administration, vascular access devices and infusion sets, types of parenteral products, components of parenteral products, parenteral packaging, convenience and needleless systems, needleless injection, extemporaneous compounding of parenteral products, infusion pumps and devices, and future parenteral dosage forms.

HISTORY AND USE OF PARENTERALS

A detailed history of early parenteral medications can be found in the first edition of this encyclopedia (2). One of the first historical references to the parenteral administration of a compound was in the late 15th century when a blood transfusion from three young boys was given to Pope Innocent VIII, resulting in the death of all four individuals. These deaths led to a ban in the use of this type of medical treatment, namely an infusion, for several centuries. It was not until the 17th century that studies on the parenteral administration of compounds was first studied in animals. The development of the hypodermic needle and the use of parenterally injected drugs in humans is first reported in the mid-19th century. By the end of this century, there was an increased interest in the use of intravenous administration of glucose and normal saline solutions. Baxter produced the first commercially prepared intravenous solutions in 1931. However, parenteral products and their administration became acceptable and a mainstay in the treatment of patients in the mid 20th century. This could be attributed, in part, to our increased understanding of microbial and viral agents, increased recognition of the dangers associated with parenteral therapy, the development of antibiotics and other drug classes, and the availability of new systems or infusion technologies. In the mid 1960s, many hospitals introduced intravenous admixture services. In the last 20 years, the area of infusion pumps and systems and improved vascular access devices has enabled parenteral therapy to extend beyond the institutional setting to clinics, ambulatory infusion centers, and home health care. In addition, the administration of parenteral drugs is also frequently utilized in basic and clinical research in animals and humans.

In today's health care environment, parenteral products are a key component of therapy for hospitalized patients. Vascular access for parenteral infusion therapy is obtained in the vast majority of hospitalized patients at some point in their therapy. There are very little data as to the use of parenteral products in today's health care environment. It was suggested that 40% of all pharmaceutical dosage forms are administered as a type of injection and that over 350 million units of large volume parenterals and 100 million units of IV admixtures (piggybacks) were used annually in the late 1980s (3). These numbers have

certainly increased since that time with the advent of new drugs and infusion methodologies. Infusion therapy in home health care continues to have a strong market in the United States. While the annual growth rate of home infusion therapy decreased between 1982 and 1993, 29% of acute care hospitals provided or were developing a home health care program. In the current market, home infusion therapy is being integrated into alternative sites, such as ambulatory infusion centers (4). Due to the rapid and increasing use of parenteral drugs, it is critical for health care providers and scientists to understand the various available dosage forms, specific products, routes of administration, catheter types, and various infusion devices. Detailed information on these devices can be found in the nursing and pharmaceutical literature (3, 5–10). In addition, company websites are a valuable source of current information, including available parenteral products, infusion sets and ports, devices and infusion pumps. A list of useful worldwide websites is shown in Table 1.

ADVANTAGES AND DISADVANTAGES OF PARENTERAL PRODUCTS

The advantages and disadvantages of parenteral drugs and administration are shown in Table 2. Generally, parenterally administered drugs are advantageous because they can provide rapid and reliable drug systemic effects, long-term drug delivery, and targeted drug delivery. The disadvantages of parenteral products are predominately associated with safety issues related to infection and thrombosis, tissue damage and/or pain upon injection, and the use of requirements for specific equipment, devices, and techniques.

ROUTES OF ADMINISTRATION

The routes of administration for parenteral products are shown in Fig. 1. The most commonly used routes are intravenous, intramuscular, subcutaneous, and intradermal. Formulations intended for administration into the central nervous system should not include preservatives. For intramuscular, intradermal, and subcutaneous, a single needle and syringe is generally used to administer the drugs. For intravenous and intra-arterial, drugs are administered using vascular access or port devices. Other parenteral routes of administration (e.g., epidural, intra-articular, and intrathecal) usually require specialized delivery sets. In some cases, the specific drug requires a specialized delivery set be utilized due to the dose of the drug or the physicochemical properties of the drug (e.g., nitroglycerin).

VASCULAR ACCESS DEVICES AND INFUSION SETS

Vascular access can be achieved through short peripheral, long dwell peripheral, central lines, and ports (8, 11). These various devices differ in their insertion, characteristics, dwell time or time they should be in place, and usage and safety features. In peripheral access, the distal veins on the hand and arm are often used, with the basilic and cephalic veins in the arms being the most common site for peripheral infusions. Alternatively, the metacarpal veins can also be utilized. The basic devices are a winged infusion device or the over-the-catheter needle, with needle sizes ranging from 16 to 26 G (20- or 22-gauge being the most common size). These catheters are usually utilized only for 48 h. A midline catheter is usually inserted into a large vein and is intended to be used over a 2- to 4- week period (Richardson). Peripherally inserted central venous catheters (PICC) are designed for long-term infusion therapy up to a year. The devices are inserted into a peripheral vein and threaded so that the tip of the catheter is within the central vascular system. Central venous catheters (CVC) are inserted into the subclavian or jugular vein and threaded until the tip is located in the superior vena cava. The types of central venous catheter are a nontunneled, Groshong, Hickman, and Brovaic. A nontunneled CVC can be inserted at the bedside, whereas the Groshan, Hickman, and Brovaic require surgical insertion. Vascular access ports (VAP) are an alternative to central venous access. These devices are surgically implanted usually into the chest wall or arm subcutaneous tissue and are composed of a rigid reservoir with a self-sealing rubber septum, and the tip of the catheter is placed into a central vein. The drug is placed into the reservoir via an injection. A VAP allows repeated, intermittent access and drug delivery (in some cases up to 2000 times), depending upon the size of the needle. Examples of these types of ports include a P.A.S Port® (SIMS Deltec), Vital-Port® (Cook Incorporated), and BardPort® and CathLink® (Bard Medical Division).

There are three basic types of intravenous administration: 1) primary set, 2) secondary set, and 3) a volume control set (Fig. 2) (8). The basic components of all these sets include a piercing spike (to insert into the bag or bottle), drip chamber and drip orifice, tubing ranging in length from 160 to 250 cm (63–98.58 in.), a roller clamp

Table 1 Representative parenteral products and devices websites

Company	Website	Products available
Abbott Laboratories	http://www.abbott.com	Premixes, IV solutions—Lifecare, injectable drug delivery systems, needleless systems, infusion pumps, Add-Vantage
Alaris Medical Systems	http://www.alarismed.com	Infusion pump systems, ambulatory pumps, needlefree systems, intravenous administration sets
Arrow International Critical Care Products	http://www.arrowintl.com	Vascular access, catheters, infusion ports
Bard Access Systems	http://www.bardaccess.com	Access systems and ports
B. Braun Medical	http://www.bbraunusa.com	IV Solutions—Excel or PAB (Partial Additive Bag), IV administration, needlefree administration, infusion pump systems, vascular access
Baxa	http://www.baxa.com	IV admixture tools, syringe infusion systems
Baxter Healthcare	http://www.baxter.com	Large and small volume parenterals, premix medications, reconstitution products and accessories, syringe pumps and sets, interlink, administration sets, infusion pumps
Becton, Dickinson and Company	http://www.bd.com	Needles, vascular access, needleless systems, catheters
Cook Endovascular	http://www.cook-inc.com	Vascular access, infusion catheters and sets
Horizon Medical Products	http://www.hmpvascular.com	Vascular access ports
I-Flow Corporation	http://www.i-flowcorp.com/home.html	Homepump infusion systems, electronic infusion pumps
SIMS Deltec	http://www.deltec.com	Access systems and ports, infusion pumps
Vygon USA	http://www.vygonusa.com	Vascular access, needleless access

Table 2 Advantages and disadvantages of parenteral drugs and administration

Advantages	Disadvantages
Useful for patients who cannot take drugs orally	More expensive and costly to produce
Useful for drugs that require a rapid onset of action (primarily intravenous administration)	Potential for infection at site of injection
Useful for emergency situations	Potential for sepsis
Useful for providing sustained drug delivery (implants, intramuscular depot injections)	Potential for thrombophlebitis
Can be used for self-delivery of drugs (subcutaneous)	Potential for fluid overload
Useful for drugs that are inactivated in the gastrointestinal tract or susceptible to first-pass metabolism by the liver	Potential for air embolism
Useful for injection of drugs directly into a tissue (targeted drug delivery)	Potential for extravasation
Useful for delivering fluids, electrolytes, or nutrients (total parenteral nutrition to patients)	Psychological distress by the patient
Useful for providing precise drug delivery by intravenous injection or infusion utilizing pharmacokinetic techniques	Require specialized equipment, devices, and techniques to prepare and administer drugs
Can be done in hospitals, ambulatory infusion centers, and in home health care	Potential for pain upon injection
	Potential for tissue damage upon injection
	Risk of needlestick injuries and exposure to blood-borne pathogens by health care worker
	Increased morbidity associated with long-term vascular access devices Disposal of needles, syringes, and other infusion devices requires special consideration

or other flow control device on the tubing, a Y-site for infusion of other components, an in-line filter (ranging from 0.2 to 170 μm) and leuk-lok adapter to attach to the vascular access device. A primary infusion set is designed to deliver solutions from the parenteral container via gravity. If an additional infusion is needed, the secondary set can be connected to the primary set via one of the Y-sites. A volume control administration set is used to deliver a small amount of solution through the use of the volume chamber. In general, administration sets are classified into macrodrip sets that can deliver 10–20 drops/ml and a microdrip set that delivers drugs at a slower rate of 60 drops/ml.

TYPES OF PARENTERAL PRODUCTS

Parenteral products can be divided into two general classes according to the volume of the product. All parenteral products are sterilized and must meet all the requirements for sterility and particulate matter and must be pyrogen-free (36). They must be prepared using strict sanitation standards in environmentally controlled areas by individuals trained to meet these standards. The injections are overfilled with a small excess over the labeled volume to ensure that the required volume can be obtained from the product. *Small-volume parenterals (SVP)* or injections are 100 ml or less and can be provided as a single- or multidose product. In contrast, *large-volume parenterals (LVP)* are intended to be used intravenously as a single-dose injection and contain more than 100 ml of solution. SVPs and LVPs are often combined during the extemporaneous preparation of intravenous admixtures, to be discussed later in this article.

The U.S. Pharmacopoeia (USP) classifies injections into five different types. The dosage form selected for a particular drug product is dependent upon the characteristics of the drug molecule (e.g., stability in solution, solubility, and injectability), the desired therapeutic effect of the product (e.g., immediate vs. sustained release), and the desired route of administration. Solutions and some emulsions (e.g., miscible with blood) can be injected via most parenteral routes of administration. Suspensions and solutions that are not miscible with blood (e.g., injections employing oleaginous vehicles) can be administered via intramuscular or subcutaneous injection but should not be given intravenously.

Parenteral products contain excipients such as buffers, solvents, nonaqueous solvents, antimicrobial preservatives, antioxidants, and chelating agents. Coloring agents are prohibited in parenteral products. All excipients must meet compendial standards, and the excipients must not interfere with the efficacy of the product (to be discussed more in detail later in this article). Parenterals are packaged in airtight containers using specific, high quality materials so that they do not interact with the product and to maintain the sterility of the product. For example, the

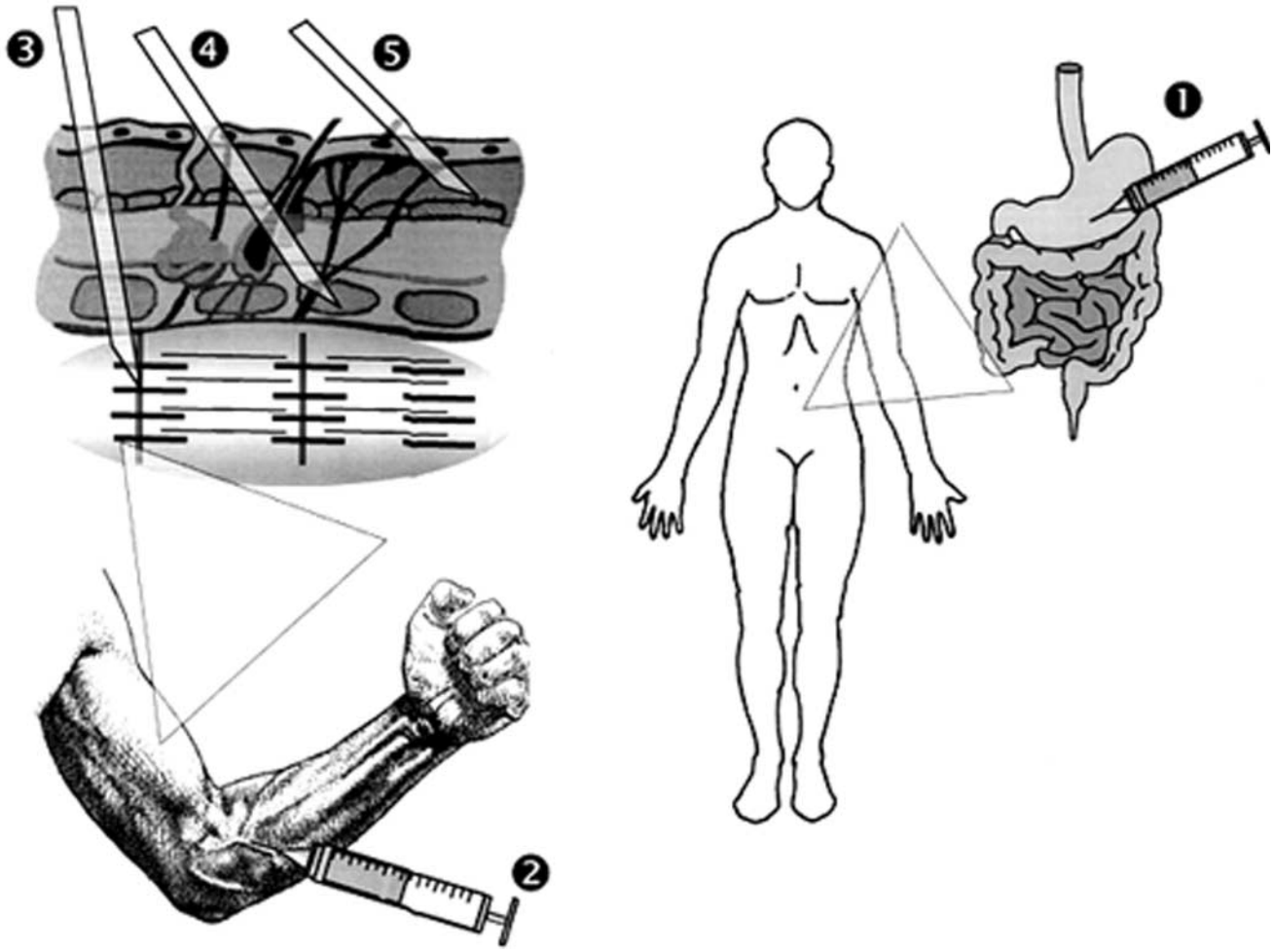

Fig. 1 Routes of parenteral administration. The following represent the most commonly used routes of administration for parenteral products: 1) intraperitoneal, 2) intravenous, 3) intramuscular, 4) subcutaneous, and 5) intradermal.

type of glass to be used in a specific parenteral drug product is indicated in the monograph. The types of packaging and containers for SVPs and LVPs will be discussed later in this article.

A SVP product is available for most of the major therapeutic classes of drug. It is often desirable for a manufacturer to provide both an oral and parenteral dosage form for a specific drug product. A "drug injection" is a liquid preparation that is composed of drug substances and or solutions. A "drug for injection" is a dry solid that upon the addition of a suitable vehicle (usually a vehicle in which the drug is stable and soluble) provides a solution that conforms to the requirements for an injection. Drugs for injection are often lyophilized or freeze-dried to assist in the reconstitution of the solid. A "drug injectable emulsion" is a liquid preparation of a drug or drug substances dissolved in a suitable emulsion vehicle. A "drug injectable suspension" is a liquid preparation of solids suspended in a suitable vehicle. A "drug for injectable suspension" is a dry solid (often lyophilized) that is intended, upon the addition of a suitable vehicle, to yield a preparation that in all aspects meets the requirements for an injectable suspension.

LVPs are often administered via intravenous infusion in a large single-dose container. The therapeutic goal of these products is to provide electrolytes, body fluids, and nutrition. These solutions may or may not be isotonic with blood depending upon the concentration of the components, which include sodium chloride, dextrose, mannitol, Ringers (sodium, potassium, calcium, and chloride) and Lactated Ringers (calcium, potassium, sodium, and lactate), sodium bicarbonate, ammonium chloride, sodium lactate, fructose, alcohol, dextran, and amino acids. Other drugs (small volume injectables) are

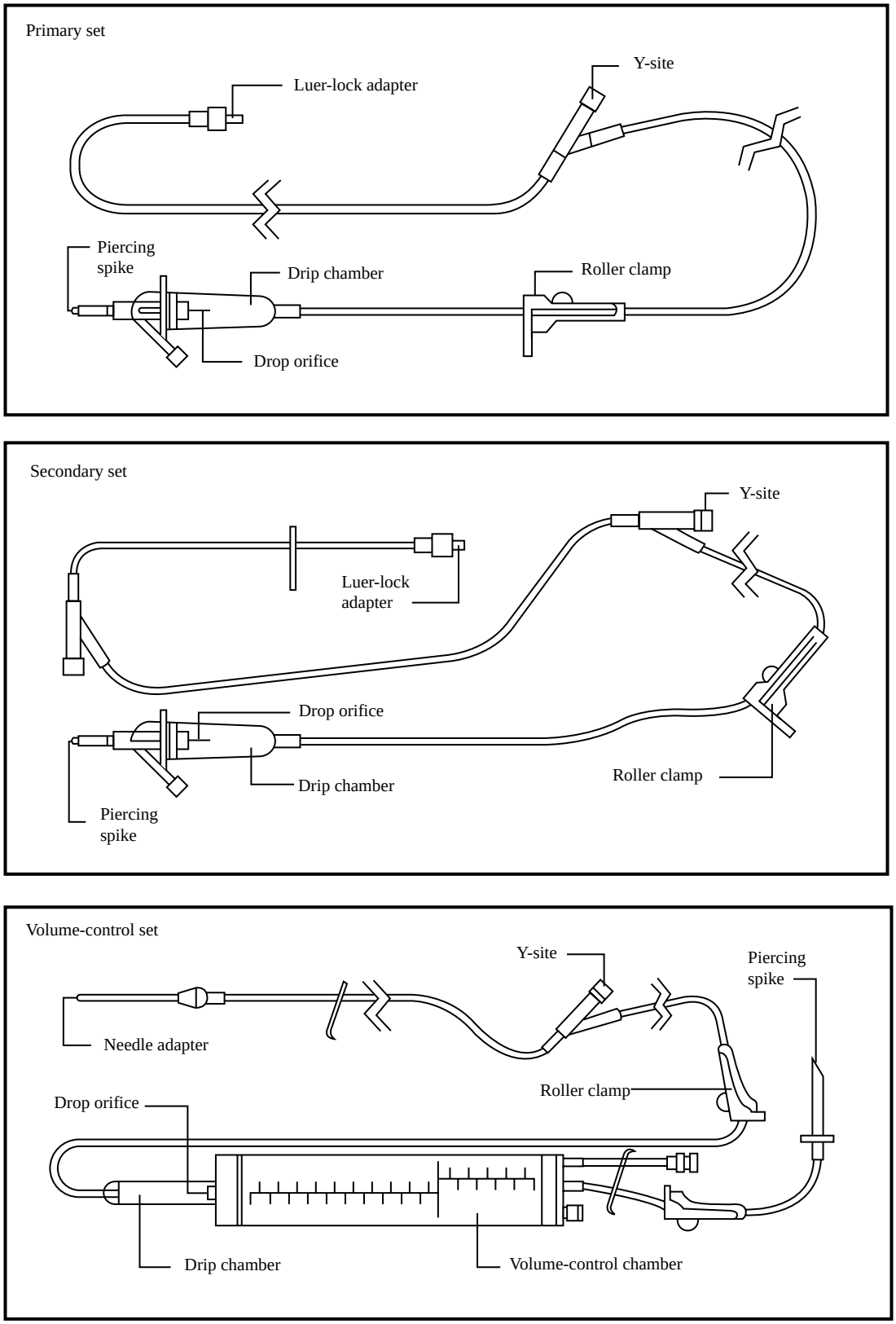

Fig. 2 Types of infusion sets used for parenteral therapy: primary, secondary, and volume-controlled infusion sets.

often combined to these LVPs, provided that these two products are compatible during the extemporaneous preparation of intravenous admixtures (discussed later).

COMPONENTS OF PARENTERAL PRODUCTS

Parenteral products are optimized during their development to provide the requisite solubility (per the required dose), stability, and syringeability. In addition, these products must meet the desired requirements for the rate of drug release based upon the dosage form and biopharmaceutical properties. Finally, it is important that parenteral products also be evaluated for their potential to cause tissue damage and/or pain associated with the injection of the formulation. The adjuvants in parenteral products can include solvents, vehicles, cosolvents, buffers, preservatives, antioxidants, inert gases, surfactants, complexation agents, and chelating agents.

It is important to understand the various types of waters used in parenteral products. The most frequently used solvent in parenteral products is Water for Injection, USP, which is not required to be sterile but must be pyrogen-free. In contrast, Sterile Water for Injection, USP is water that has been sterilized, does not include a preservative or antimicrobial agent, is pyrogen-free, and is provided in single containers no larger than 1000 ml. The use of this product is for the reconstitution of other parenteral products, in most cases antibiotics. This product must not be given alone. Bacteriostatic Water for Injection, USP is sterile water that can contain one or more preservative or antimicrobial agent (specified on the label) and is packaged in prefilled syringes or vials that are no larger than 30 ml. It is also used in the reconstitution of SVPs. The limitation with Bacteriostatic Water for Injection, USP is the presence of the antimicrobial agent that is contraindicated in newborns. Other solvents used for parenteral formulations are Sodium Chloride Injection, USP and Bacteriostatic Sodium Chloride Injection, USP, Ringers Injection, USP, and Lactated Ringer's, USP.

Other vehicles may be added to parenteral products if the aqueous solubility is limited. However, these vehicles must be nontoxic, nonsensitizing, and nonirritating (3, 6). In addition, these solvents must be compatible with the drug and other components in the formulation. Cosolvents often used in parenteral formulations include propylene glycol, ethanol, polyethylene glycols, glycerin, and dimethylacetamide. In addition, fixed vegetable oils, such as peanut, cottonseed, sesame and castor oil, can be used; however the USP provides clear restrictions on their use in parenteral products.

Buffers can also be provided in parenteral formulations to ensure the required pH needed for solubility and/or stability considerations. Other excipients included in parenteral products are preservatives (e.g., benzyl alcohol, ρ-hydroxybenzoate esters, and phenol), antioxidants (e.g., ascorbic acid, sodium bisulfite, sodium metabisulfite, cysteine, and butyl hydroxy anisole), surfactants (e.g., polyoxyethylene sorbitan monooleate), and emulsifying agents (e.g., polysorbates). An inert gas (such as nitrogen) can also be used to enhance drug stability. Stability and solubility can also be enhanced by the addition of complexation and chelating agents such as the ethylenediaminetetraacetic acid salts. For a more detailed list of approved excipients in parenteral products, the reader should consult the monographs within the USP.

PARENTERAL PACKAGING

In general, all parenteral products must be manufactured under strict, current good manufacturing processes (cGMP) to ensure the final product is sterile and pyrogen-free. Sterilization is defined as the complete destruction of all living organisms or their spores or the complete removal from the product (6). Pharmaceutical products can be sterilized by steam sterilization, dry-heat sterilization, filtration sterilization, gas sterilization, and ionizing-radiation sterilization. The USP provides monographs and standards for biological indicators required to test the validity of the sterilization process. These products must also be tested for pyrogens—fever-producing substances that arise from microbial contamination most likely thought to be endotoxins or lipopolysaccharide in the bacterial outer cell membrane.

Injections are provided in either multiple-dose containers or single-dose containers. A multiple-dose container is often a vial that will allow the withdrawal of successive portions of the contents without a change in the strength of the product and while maintaining the sterility. A single-dose product is intended for a single parenteral administration. These products can be an ampul, vial, or a syringe. For some drugs, there are specific double-chambered vials that contain the reconstitution solvent and the powdered drug (e.g., Mix-O-Vial—to be discussed later). Types I, II, and III glass are required for parenteral products and are specified in the individual monograph for a given drug.

Ampuls are utilized for a single dose and, as such, do not require a preservative. However, in many cases, the manufacturer will include a preservative, as the drug formulation is the same for both the ampul and

multiple-dose vial. The disadvantages of ampuls are that these containers become contaminated with glass particles when opened and require the use of a syringe to remove the drug solution. A filter needle must be used sometime during the withdrawal of the solution or delivery of the drug solution to a flexible bag or other intravenous solution to ensure the glass is removed from the solution. Ampuls are opened via breaking the neck at a prescored position.

Vials can be used for single or multiple doses. The glass containers are sealed with rubber closures that permit the withdrawal of the drug solution via a syringe. The disadvantage of these systems is associated with ensuring that the drug solution is compatible with the rubber closure. Furthermore, when utilizing vials in the extemporaneous preparation of sterile intravenous admixtures, the health care practitioner must minimize the potential of coring during the introduction of the needle through the rubber seal. Furthermore, there is always the concern of contamination of the solution with repeated withdrawals. The potential for contamination can be minimized by the use of single-dose vials.

Parenteral solutions can also be packaged in syringe dosage forms for a single-dose use. As such, they can be considered a type of convenience container (to be discussed later). The syringe and needle are sterile until opened. They are ideal for emergency situations or the home health care environment.

LVPs are usually provided in glass containers, flexible plastic bags, or semirigid containers. These systems are also classified as open systems (nonvacuum) and closed systems (vacuum). The largest manufacturers of LVPs are Abbott Laboratories, Baxter Healthcare Corporation, and B. Braun.

Glass containers are sealed with a thick rubber disk and a target in the center for the piercing spike. Glass bottles can be either vented with a plastic venting tube or nonvented, thereby requiring either a nonvented administration set or a vented administration set, respectively. The advantages of glass containers for parenterals are that they are easy to sterilize, can be accurately read, and are generally inert and less susceptible to incompatibilities with drugs or leaching of components compared to the plastic flexible intravenous bags. The disadvantage of glass is associated with handling the glass bottles and the potential for breakage (10).

Plastic intravenous fluid containers were first introduced due to the need to start intravenous therapy while transporting soldiers from the battlefield or triage area to the hospitals. These containers are flexible due to the presence of plasticizers, with the bags being composed of polyvinyl chloride. In contrast, semirigid containers are often composed of polyolefin. Some representative shapes of these various types of containers are shown in Fig. 3. The most common manufacturers of intravenous solutions are Abbott Laboratories—Lifecare, Baxter Healthcare—Viaflex, and B. Braun Medical—Excel. The major advantages of plastic flexible bag systems for parenterals are that they do not require the use of a vented administration set as they collapse when empty, and they are less susceptible to breakage. It is also easier to store and transport these bags. The difficulties with these flexible plastic bags for infusions solutions are the potential for incompatibilities of the drug substance with the components in the bag (see later), the potential for the bag to get perforated during its use, thus compromising the sterility of the solution, and the difficulty in reading the volume remaining in the bag. One major concern with the use of flexible plastic bags is the potential for the drug compound to leach out the plasticizers from the systems. Semirigid containers are similar to flexible plastic containers in that they are lightweight and nonbreakable and can be easily transported and stored. These containers are less likely to be perforated during their use. More importantly, these containers do not contain plasticizers and, as such, may be more compatible with drug substances. The disadvantages are related to their similar properties to glass containers, in that they require venting, can be more susceptible to cracking upon extreme changes in temperature, should not be frozen, and do not adapt well for ambulatory care.

CONVENIENCE AND NEEDLELESS SYSTEMS

Whereas the compounding and administration of parenteral products and intravenous admixtures continues to be a vital and important component in the care of hospitalized and home health care patients, there is continued interest in easing the preparation, storage, and administration of these products with respect to controlling contamination of the finished product and protecting the health care providers from needlestick injuries. It is estimated that more than 750,000 needlestick injuries occur every year. Commonly used convenience and/or needleless systems include premixes, bags, and vial systems (e.g., Add-Vantage and Mini-Bag Plus®), prefilled syringe systems (Carpuject®—Abbott and Tubex®—Wyeth-Ayerst) and double-chambered vial systems (Mix-O-Vial—Pharmacia-Upjohn and Redi-Vial®—Lilly).

For drugs with suitable stability in intravenous solutions, premixes provide an alternative to the

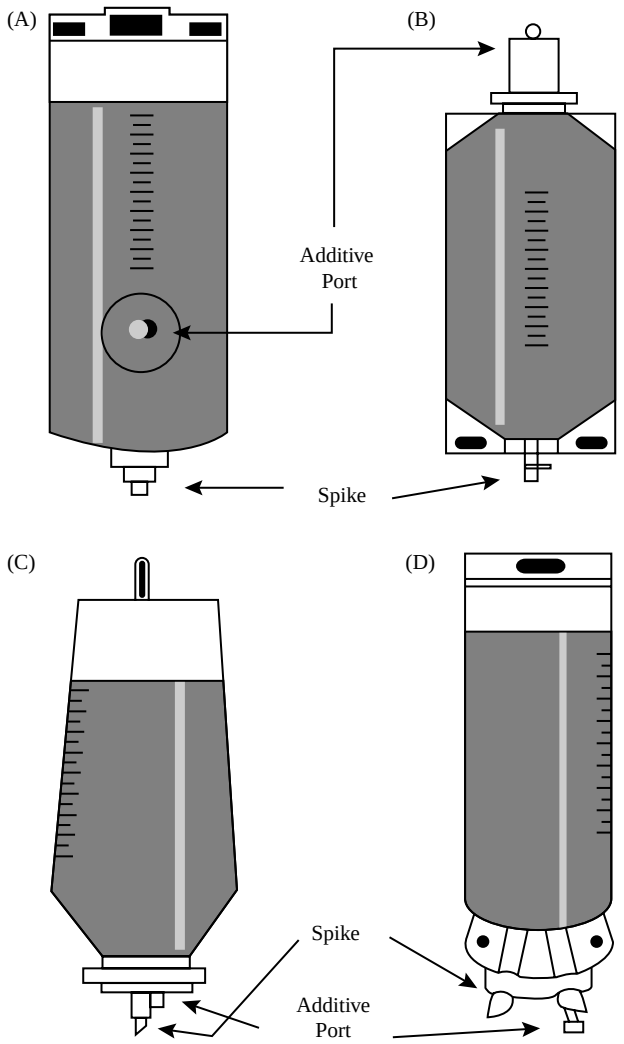

Fig. 3 Types of large volume parenterals. These represent the various types of flexible intravenous bag systems: (A) Lifecare® by Abbott Laboratories, (B) Representative vial and flexible IV bag system, such as the Add-Vantage®—Abbott Laboratories or Mini-Bag Plus System®—Baxter Healthcare, (C) Excel®—B. Braun Medical, and (D) Viaflex®—Baxter Healthcare. These bags contain either polyvinyl chloride (Lifecare or Viaflex) or polyolefin (Excel).

extemporaneous compounding of admixtures. These products are ready to administer, reduce the chance for a medication error, reduce the potential for infection, and decrease the chance for needlestick injuries. In addition, there is an advantage in using these products with respect to the shelf-life of the product. The stability and storage requirements for each product is provided by the manufacturer. For example, the FirstChoice® Premix products (Abbott) in the overwrap have a shelf-life of, typically, 18 months, whereas those products in which the overwrap has been removed and which are stored at room temperature can be stable for up to 30 days, provided no additional drugs or additives have been added to the product. The diluents in these premix products include 0.45 or 0.9% sodium chloride, 5% dextrose, water for injection, Lactated Ringers, and combinations of these diluents in volumes ranging from 50 to 1000 ml in plastic or glass containers. Drug classes that are currently formulated as premixes include amino acids, dextrans, electrolytes, cardiovascular, anti-infectives, analgesics, and gastrointestinal and respiratory compounds.

The Add-Vantage® system (Abbott Laboratories) and the Mini-Bag® Plus system (Baxter Healthcare) are needleless drug delivery systems composed of a drug-containing vial and a diluent in a flexible plastic intravenous bag. A schematic of these type of systems is shown in Fig. 3B. The drug in the vial comes in contact with the diluent, followed by the drug being transferred back into the bag with the vial still attached; this system can then be attached directly to the infusion equipment. In the Add-Vantage system®, there are specialized vials and intravenous bags and it is necessary for the health care professional to activate the system by removing the vial stopper, thus allowing the diluent to enter the vial. The Mini-Bag Plus® system is designed to allow the simple reconstitution of standard 20 mm powdered drug vials. The Monovial Safety Guard® (Becton, Dickinson and Company) is an integrated, self-contained system that allows the transfer of a reconstitution solution from a flexible intravenous bag or vial into a drug-containing vial, and it is only available for a limited number of drugs.

As such, the advantages of these systems are that the product can be easily stored and quickly prepared without the need for calculations, specialized equipment (such as laminar airflow hoods) or needles and syringes. They also allow for a quicker turnaround time for the first dose. These products enhance safety for both the patient, by reducing the chance for medication errors (e.g., the wrong drug added to the vial, the incorrect amount of drug to be added to the bag, or a product being incorrectly labeled), and for the health care practitioner, by minimizing the chance for a needlestick injury. In addition, these products can help to reduce costs associated with unused doses because the unwrapped products can be redistributed for short periods of time. At present, a variety of therapeutic classes of drugs from anti-infectives to cardiovascular agents to pain management at various doses are available for reconstitution in bags containing 0.9 or 0.45% sodium chloride or 5% dextrose in 50- to 250- ml bags.

Prefilled syringes (Carpuject®—Abbott and Tubex®—Wyeth-Ayerst) are composed of drug solutions placed in a

syringe with a needle and needleless systems. The advantages of these systems are the convenience associated with a standard dose, less chance for medication error associated with extemporaneous compounding of these syringes, usefulness in emergency situations, and ease of storage. The needle and syringe are sterile until opened. Prefilled syringes are available for drugs ranging from anti-infectives, analgesics, and antipsychotics to antiemetics.

Doubled-chambered vials are advantageous in that the reconstitution solution is separated from the drug until desired by the health care practitioner. The Mix-O-Vial® (Pharmacia-Upjohn) system is a combination of a powdered or lyophilized drug in a lower container and an appropriate diluent with a preservative and other active ingredients in an upper container. Following removal of the dust cover and upon pressure on the top plunger, the solution comes in contact with the drug and the vial is shaken until a solution is obtained. The upper plunger can then be swabbed with a disinfectant and the appropriate volume of drug removed with a needle as in the standard preparation of an intravenous admixture using a vial.

With an increased interest in eliminating needlestick injuries associated with parenteral drug administration in health care workers, needleless systems are becoming more common in patient care. For example, the Interlink® System (Baxter) is designed for needleless access during intravenous therapy. These types of products are available for injection sites, Y-sites, vial adapters, infusion and vein access, syringe products and catheter extension sets. Other needleless catheters and infusion sites include the Introcan® Safety IV catheter and the Sifesite® injection caps (B. Braun).

NEEDLELESS INJECTION

The concept of needleless injection is not a new one and has been thought about since the 1940s. Current products utilize either spring action or compressed gas (e.g., helium or carbon dioxide) as a propellant to deliver a drug through the skin. These needleless systems offer several advantages. The first potential advantage is reduced pain and anxiety, an advantage for use in children. The second advantage is that needleless injection causes less tissue damage than conventional needles (12). Finally, a needleless system results in a diffuse pattern of exposure and, therefore, increases surface area and absorption rate (12). The main disadvantage of this system is unreliability in reference to pain and discomfort and skin characteristics that can influence the amount of drug entering the body (12). This system has been used to administer vaccines, insulin (12), and drugs for topical applications (e.g., penile erectile dysfunction) (13) and as a means to deliver DNA for gene therapy (14).

EXTEMPORANEOUS COMPOUNDING OF PARENTERAL PRODUCTS

Whereas the presence of the various convenience parenteral products has assisted health care practitioners in safely and accurately delivering drugs to the patients, the extemporaneous compounding of parenteral products continues to be an important component in institutional settings and home health care (3, 5, 15). Parenteral intravenous admixtures include the withdrawing of the drug solution from an ampul(s) or vial(s) and placing it into various large volume solutions, syringe dosage forms for patients, total parenteral nutrition solutions and cassettes, or other delivery systems for home health care patients. The American Society of Health-System Pharmacists, the National Association of Boards of Pharmacy, and the USP provide practitioners with useful technical assistance bulletins, rules, and standards for the preparation of parenteral products (13). The concerns associated with the extemporaneous preparation of parenteral products are maintaining sterility of the products through proper aseptic techniques, calculating and providing the correct dosage, preventing or reducing drug–drug, drug–solution, or drug–container incompatibilities during the preparation or administration of the product, and maintaining and providing drug stability and quality control.

The majority of extemporaneous parenteral products are prepared by pharmacists working in hospitals, home health care, or long-term care facilities. These products must be prepared using aseptic technique and using the appropriate supplies (e.g., syringes, needles, and filter needles, and caps) and equipment (Class 100 laminar airflow hoods enclosed within a class 10,000 clean room). Aseptic technique which differs from sterilization, is a process by which an individual can manipulate sterile products and containers to prevent microbial contamination. Pharmacists and other personnel involved in the extemporaneous preparation of parenteral products require special knowledge and training and should receive additional training and education on a routine basis to ensure proper aseptic techniques are being followed consistently. In addition, these individuals must be able to perform the required calculations (e.g., dosing,

milliequivalents, milliosmoles, and powder volume) needed to prepare intravenous admixtures. Equally important to the safe preparation of intravenous admixtures is an understanding of general principles and concepts related to drug and solution or container incompatibilities and to drug stability and also specific knowledge as to whether a specific drug is compatible or stable with another drug, solution, or container. For example, general and specific information on intravenous admixture incompatibilities can be found in books such as Handbook on Injectable Drugs (16, 17) and King Guide to Parenteral Admixtures (18) and in primary literature sources such as the American Journal of Health-System Pharmacy and the International Journal of Pharmaceutical Compounding.

INFUSION PUMPS AND DEVICES

Infusion pumps and devices are an essential component to the delivery of parenteral drugs, particularly those given by the intravenous route. For drugs that are administered via intravenous infusion, there are two forces that control fluid flow: 1) the pressure of an active force of the liquid that can be generated via gravity flow (viz., hydrostatic pressure) or mechanically via a positive pressure pump and 2) resistance, or an opposing force, that is generated via the infusion sets, a vascular access device and/or blood vessels. The maximum flow rate will depend upon the ratio of the change in pressure exerted by the liquid to that of the change in resistance.

An infusion control device (ICD) is a device that maintains a constant infusion rate in a gravity flow system (controller) or via a positive pressure pump. A positive pressure pump is a device that provides mechanical pressure (2–12 psi) to overcome the resistance to flow in the vessels. The types of positive pressure pumps are categorized according to how they deliver the solution and their degree of precision in the flow rate. Positive pressure pumps include peristaltic pumps, cassette pumps, syringe pumps, nonelectric or disposable pumps, and patient-controlled analgesic pumps (PCA). Syringe pumps are usually the most accurate pumps, with flow variances at 2% or less. Nonelectric or disposable syringe and PCA pumps are useful for ambulatory care. PCA pumps are very useful for the parenteral administration of analgesics (viz., morphine) and can be easily programmed to deliver bolus doses and provide a dosing history. Nonelectric or disposable pumps (e.g., Homepump®—I-Flow Corporation, Readymed®—Alaris Medical Systems, and SmartDose®—ProMed) are lightweight, and the solution is delivered based upon a vacuum or through the generation of a gas in the system. A recent consensus development conference on the safety, cost, simplicity of use, and training of intravenous drug delivery systems, focusing on acute care and nonelectronic devices, reviewed the use of manufacturer-prepared (e.g., premixed or frozen products), point-of-care activated systems (manufacturer-prepared products that require the drug and diluent to be mixed at the point of care), pharmacy-based intravenous admixture, intravenous push medications in prepared or premade syringes, augmented iv push systems (syringe pumps), and volume control chambers (19). Manufacturer-prepared products, point-of-care activated products, and pharmacy-based intravenous admixture programs were recommended as being superior intravenous drug delivery systems, with the manufactured products being considered the safest systems due to the quality assurance in the preparation of these products.

FUTURE PARENTERAL DOSAGE FORMS

Current research is leading to newer types of parenteral dosage forms that will be useful for both immediate and sustained drug delivery, for systemic and targeted drug delivery, and for the delivery of small molecules and macromolecules (e.g, proteins, peptides, and DNA). There has been an increased interest in developing a wide variety of particulate drug delivery systems for parenteral products, which have included liposomes or other phospholipid vesicles, microspheres, microcapsules, nanoparticles, or microemulsions (20–23). The development of new biomaterials, such as the linear and branched biodegradable polyesters, has increased the interest in the development of these systems for microsphere formulations for parenteral drugs (24, 25). An advantage is that drug molecules can be incorporated into these particulate carriers, and, as such, the rate of drug release can be modified, cellular uptake can be facilitated, or the degree of tissue damage or pain can be reduced.

Microemulsions, defined as clear solutions obtained by tritrating normal coarse oil-in-water emulsions with a medium chain alcohol and composed of the nonpolar phase, surfactant and cosurfactant, appear to be potentially useful for parenteral administration, as these are clear and stable formulations that are able to be filtered and might be suitable for intravenous administration (21, 22). In addition, other researchers are investigating in situ forming gel or implants that can be easily injected intramuscularly or subcutaneously and that result in the formation of a depot at the site of injection with the

potential to modify or extend the release of the drug or macromolecule (25–27).

CONCLUSIONS

Parenteral products will continue to play a vital role in the treatment of patients when the oral route is contraindicated, when it is necessary to carefully control drug blood levels in response to therapeutic effects, when a prolonged therapeutic effect is needed through a long-acting injectable, or when a drug effect is to be targeted to a specific tissue or organ, to name a few instances. Advances in the technology required for the administration of parenteral dosage forms in the last 100 years have expanded their clinical uses for in-patient and out-patient settings. In addition, there is improved convenience and safety for the health care providers who prepare and administer these products. It seems likely that more parenteral dosage forms will become available in the marketplace in response to the compounds being developed through biotechnology.

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